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CLINICAL STUDY PROTOCOL

Randomized, Open-Label, Multicenter Trial of the Safety and Effectiveness of Oral Telithromycin (Ketek®) and Amoxicillin/Clavulanic Acid (Augmentin®) in Outpatients With Respiratory Tract Infections in Usual Care Settings

HMR3647A/3014 Telithromycin

30 '7 Protocol, 7/27/01

Multicenter study

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PROTOCOL OUTLINE

Study number HMR3647A/3014

Title

Randomized, Open-Label, Multicenter Trial of the Safety and Effectiveness of Oral Telithromycin (Ketek®) and Amoxicillin/Clavulanic Acid (Augmentin®) in Outpatients With Respiratory Tract Infections in Usual Care Settings

Investigator(s), study site(s)

Multicenter study (US, Canada)
Coordinating investigator: Paul Ianinni, MD, Danbury Hospital, Department of Medicine, 24 Hospital Ave, Danbury, CT 06810. USA

Study duration and dates	Five to eight months, with subject recruitment proposed to start in October 2001.	**Phase**	III

Objectives

- To characterize the safety and effectiveness of telithromycin when used for the treatment of community-acquired respiratory tract infections in a large population of outpatients in a usual care setting.
- To compare the effectiveness of telithromycin and amoxicillin/clavulanic acid in the treatment of community-acquired respiratory tract infections in a large population of outpatients in a usual care setting.

Study design

Comparative, randomized (1:1), open-label, multicenter study.
Subjects with community-acquired pneumonia (CAP) or acute exacerbation of chronic bronchitis (AECB) will receive either telithromycin for 7 to 10 days or amoxicillin/clavulanic acid (AMC) for 7 to 10 days. Subjects with acute sinusitis (AS) will receive either telithromycin for 5 days or AMC for 7 to 10 days.
Visits will be performed at baseline on Day 1 at the start of treatment (Visit 1, pre-therapy/entry), between Days 17 and 22 (Visit 2, post-therapy), and between Days 30 and 35 (Visit 3, late post-therapy). Safety and effectiveness will be assessed at Visits 2 and 3.
Subjects withdrawn from the study will not be replaced.

Number of subjects

Approximately 24,000 subjects, randomized to telithromycin or AMC on a 1:1 basis. Subjects ≥50 years will constitute at least 35% of the total number of subjects enrolled.

Inclusion criteria

Adult outpatients (men or women) ≥18 years of age who fulfill clinical diagnostic criteria (investigator's diagnosis) for CAP, AECB or AS.

Treatments

Telithromycin: 800 mg qd orally for 7 to 10 days for CAP or AECB, or 800 mg qd orally for 5 days for AS. In subjects with known severe renal impairment (creatinine clearance <30 mL/min), the dose will be reduced to 400 mg qd.
AMC: 875/125 mg bid orally for 7 to 10 days. In subjects with known severe renal impairment, the dose will be reduced to 500 mg amoxicillin (500/125 mg tablet) bid if creatinine clearance is between 10 and 30 mL/min, and to 500 mg qd if creatinine clearance is <10 mL/min.

Safety analysis

Based on rates of serious and non-serious adverse events. At Visits 2 and 3, the investigator will determine if serious adverse events (SAEs) or adverse events of special interest occurred. The occurrence of an SAE or an adverse event of special interest will prompt a follow-up investigation, as outlined in an "Adverse event of interest" form provided to the investigator. Clinical laboratory tests will be conducted at Visit 1 (baseline) and Visit 2.

Effectiveness analysis

Occurrence of hospitalization and whether hospitalization was for a complication of the primary infection or for an adverse event, prescription of an additional antibiotic to treat the primary infection, and the time lost from work (if the subject is employed).

Statistical procedures

Baseline demographic and clinical variables will be summarized and compared between treatment groups.
Safety analysis (all subjects treated with study medication and with at least one post baseline safety assessment): The safety analysis will include rates of serious and non-serious adverse events occurring during the 30-day study period. Confidence interval estimates for event rates will be calculated. Event rates will also be summarized by subpopulations of subjects potentially at risk, including women, older subjects (≥50 years), subjects with renal or hepatic impairment, subjects with cardiovascular or chronic respiratory diseases, and subjects taking selected concomitant medications.
Effectiveness analysis (ITT population): Summary statistics and confidence intervals will be determined by treatment group for each of the effectiveness variables. Comparisons will be made between treatment groups to establish the clinical non-inferiority of telithromycin, with the comparison of special interest being rates of hospitalization in subjects ≥50 years.

An interim analysis will be carried out after the first 6,000 subjects treated with telithromycin have completed the study.

STUDY SCHEDULE

Study Procedure	Visit 1 Pre-therapy/ entry (Day 1)	Visit 2 Post-therapy (Day 17 to 22)	Visit 3 Late post-therapy (Day 30 to 35)
Informed consent	X		
Inclusion/exclusion criteria	X		
Demographics	X		
Medical history	X		
Pregnancy test for women of childbearing	X		
Document concomitant medications	X	X	X
Dispense study medication	X		
Clinical laboratory tests	X	X	
Safety evaluation		X	X
Effectiveness evaluation		X	X
Document date of first and last dose of study		X	

ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
AECB	Acute exacerbation of chronic bronchitis
ALT	Alanine transaminase
AMC	Amoxicillin/clavulanic acid
AS	Acute sinusitis
AST	Aspartate transaminase
bid	Twice-daily dosing
CAP	Community-acquired pneumonia
CFR	Code of Federal Regulations (USA)
CRO	Contract research organization
ECG	Electrocardiogram
EU	European Union
GCP	Good clinical practice
ICH	International conference on harmonization
ICU	Intensive care unit
IEC	Independent ethics committee
IRB	Institutional review board
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
qd	Once-daily dosing
QT	QT interval on the electrocardiogram
QTc	QT interval corrected according to Bazett's formula
rRNA	Ribosomal nucleic acid
RTI	Respiratory tract infection
SAE	Serious adverse event
WHO	World Health Organization

1 INTRODUCTION AND STUDY RATIONALE

1.1 INTRODUCTION

Telithromycin is the first in a new class of antimicrobial agents, the ketolides. Telithromycin has been developed for the treatment of community-acquired respiratory tract infections (RTIs) because its antibacterial spectrum covers all the key respiratory pathogens, including strains resistant to macrolides, and because its pharmacokinetics permit a once-daily treatment regimen. It is active in vitro against the major organisms encountered in RTIs, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Streptococcus pyogenes*, anaerobic bacteria, and atypical pathogens such as *Mycoplasma pneumoniae* and intracellular pathogens such as *Legionella pneumophila* and *Chlamydiophila (Chlamydia) pneumoniae*.

Telithromycin is derived from erythromycin A and has a unique mechanism of action that accounts for its activity against macrolide-resistant pathogens. It binds to domain II of the 23s rRNA of the 50s ribosomal subunit and interferes with assembly of the 30s ribosomal subunit. Telithromycin also exhibits the additional ribosomal activity associated with macrolides: binding to domain V of the 23s rRNA and disruption of the assembly of the 50 ribosomal subunit. This novel mechanism of action results in outstanding activity against sensitive strains of *S. pneumoniae*, far more potent than that of macrolides, as well as potent activity against macrolide-resistant strains. There is no cross-resistance to beta-lactam or quinolone antibiotics.

The efficacy and safety of telithromycin were assessed in 3,265 subjects with RTIs (community-acquired pneumonia [CAP], acute bacterial sinusitis [AS], acute exacerbation of chronic bronchitis [AECB], and tonsillitis/pharyngitis due to *S. pyogenes*). A 5-day regimen was used for AS, AECB and tonsillitis/pharyngitis and a 7- to 10-day regimen was used for CAP. Efficacy equivalent to frequently used, marketed antibiotics, which are dosed more frequently and for a longer period of time, was observed in these subjects. Efficacy was also demonstrated in CAP outpatients with bacteremia, in AECB subjects with severe bronchial obstruction, and in subjects at risk for morbid sequelae.

The safety profile of telithromycin was comparable to that of other commonly used antibiotics, and in particular to that of the macrolides. The incidence of gastrointestinal adverse events, while slightly higher than that of the new macrolides, fell within the range of marketed antibiotics. There was no evidence of excess risk of hepatic adverse events. Treatment with telithromycin, which has a weak inhibitory effect on the cardiac Ikr channel, was associated with a small (approximately 1 ms) change in the electrocardiographic QT interval (corrected for heart rate). No excess in adverse cardiovascular events was observed with telithromycin administration.

Telithromycin is metabolized partially by cytochrome P450 (CYP3A4). Concomitant administration with a potent inhibitor of this enzyme, ketoconazole, was associated with a modest elevation in plasma concentrations of telithromycin. No excess in adverse events was observed in telithromycin-treated subjects who received concomitant therapy with CYP3A4 inhibitors.

Further details can be found in the Investigators' Brochure [1], which contains comprehensive information on telithromycin.

1.2 RATIONALE

Simplified large-scale clinical studies provide an opportunity to study the effectiveness and safety of drugs in usual care settings and in diverse populations. The data obtained can then permit a better assessment of the probable performance of the drug after it has been marketed. Accordingly, this study will assess the safety and effectiveness data for telithromycin in a usual care setting in a large and diverse population of subjects, including older subjects (≥50 years) and subjects with multiple underlying diseases. The potential for rare adverse events, which are difficult to evaluate in smaller numbers of subjects, will also be evaluated.

Amoxicillin/clavulanic acid (AMC) was chosen as a comparator because of its excellent activity against the three main pathogens encountered in RTIs (i.e., *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*). In addition, AMC retains activity against strains of *S. pneumoniae* that are resistant to penicillin. It is also effective against strains of *S. pneumoniae* that are resistant to erythromycin, and is therefore used in areas of high prevalence of *S. pneumoniae* resistance to erythromycin. AMC has been used extensively worldwide and has a well-characterized safety profile, e.g., [2,3,4].

This study will be performed in North America, with safety and effectiveness data evaluated from approximately 24,000 subjects (12,000 subjects treated with telithromycin and 12,000 subjects treated with comparator). An interim analysis will be carried out after the first 6,000 subjects treated with telithromycin have completed the study.

2 STUDY OBJECTIVES

- To characterize the safety and effectiveness of telithromycin when used for the treatment of community-acquired respiratory tract infections in a large population of outpatients in a usual care setting.

- To compare the effectiveness of telithromycin and amoxicillin/clavulanic acid in the treatment of community-acquired respiratory tract infections in a large population of outpatients in a usual care setting.

3 STUDY DESIGN, DURATION AND DATES

3.1 STUDY DESIGN

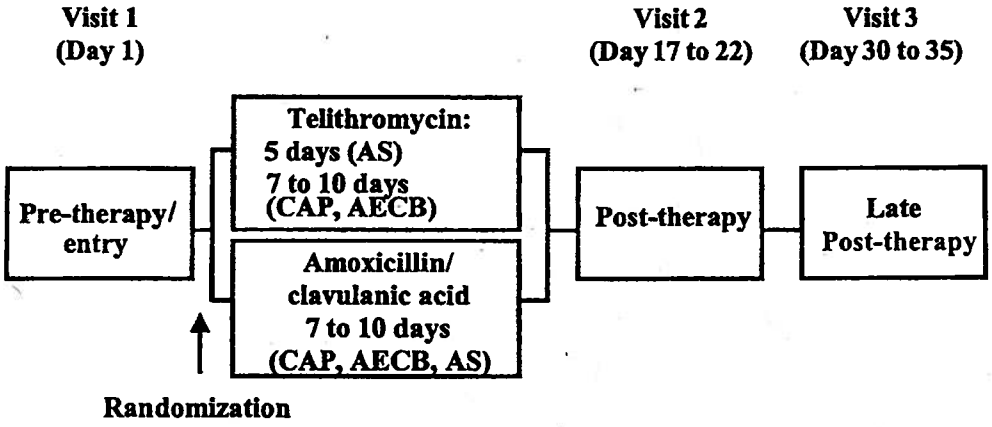
This is a comparative, randomized (1:1), open-label, multicenter study.

Subjects with CAP or AECB will receive either telithromycin for 7 to 10 days or amoxicillin/clavulanic acid (AMC) for 7 to 10 days.

Subjects with AS will receive either telithromycin for 5 days or AMC for 7 to 10 days.

In all indications the dose of telithromycin will be 800 mg qd and the dose of AMC will be 875/125 mg bid, except in cases of known severe renal impairment, when the doses of both study medications will be reduced (see *Section 5.2*).

Visits will be performed at baseline on Day 1 at the start of treatment (Visit 1, pre-therapy/entry), between Days 17 and 22 (Visit 2, post-therapy), and between Days 30 and 35 (Visit 3, late post-therapy), as summarized in the figure below. Safety and effectiveness will be assessed at Visits 2 and 3.



Subjects withdrawn from the study will not be replaced.

An interim analysis will be carried out after the first 6,000 subjects treated with telithromycin have completed the study (see *Section 11.4*).

3.2 STUDY DURATION AND DATES

The duration of this study is expected to be five to eight months, with subject recruitment proposed to start in October 2001. The actual overall study duration or subject recruitment period may vary.

4 SELECTION OF SUBJECTS

4.1 NUMBER OF SUBJECTS

As calculated in *Section 11.5*, approximately 24,000 subjects (randomized to telithromycin or AMC on a 1:1 basis) should be enrolled and treated in this study. It is planned to recruit this sample in approximately 2,000 to 5,000 centers. The recommended number of subjects per center is 4 to 50. Subjects ≥50 years will constitute at least 35% of the total number of subjects enrolled (i.e., approximately 4200 subjects in the telithromycin group). Enrollment into the screening or randomization phase of the study will be stopped when the anticipated or actual subject numbers have been achieved across both age groups (18 to 49 and ≥50 years).

4.2 INCLUSION CRITERIA

Subjects meeting all of the following criteria will be considered for enrollment into the study:

- Adult outpatients (men or women) ≥18 years of age
- Fulfillment of clinical diagnostic criteria (investigator's diagnosis) for one of the following indications:
  - CAP
  - AECB
  - AS

Informed consent must be obtained in writing for all subjects at enrollment into the study (see *Section 12.3*).

4.3 EXCLUSION CRITERIA

Subjects presenting with any of the following will not be included in the study:

- Subjects with a known history of congenital long-QTc syndrome
- Pregnant or breast-feeding
- Hypersensitivity to telithromycin, or beta-lactam or macrolide classes of antibiotics
- Treatment required during the study with ergot alkaloid derivatives, terfenadine, cisapride, astemizole, pimozide
- Previous participation in this study
- Subjects with a previous history of cholestatic jaundice/hepatic dysfunction associated with AMC.

Any waiver of these inclusion and exclusion criteria must be approved by the investigator and the sponsor on a case-by-case basis prior to enrolling the subject. This must be documented by both the sponsor and the investigator.

4.4 SUBJECTS OF REPRODUCTIVE POTENTIAL

Women who are pregnant or breast feeding will be excluded from this study.

Women of childbearing potential must take a urine pregnancy test at Visit 1 before taking any study medication.

5 STUDY TREATMENTS

5.1 DETAILS OF STUDY TREATMENTS

Drug code:	HMR3647	-
INN:	Telithromycin	Amoxicillin/clavulanic acid
Formulation:	Tablets containing 400 mg of telithromycin (Ketek®)	Tablets containing 875 mg of amoxicillin and 125 mg of potassium clavulanic acid (Augmentin® 875/125)
Manufacturer:	Aventis Pharma	GlaxoSmithKline

Subjects with known severe renal impairment will receive reduced doses of study medication (see *Section 5.2*). In the case of amoxicillin/clavulanic acid, 500/125 mg tablets (Augmentin® 500/125) will be used, which will be prescribed by the investigator as the commercially available product.

The study medication should be stored at 25°C (77°F), excursions to 15 to 30°C (59 to 86°F) are permitted.

5.2 DOSAGE SCHEDULE

All subjects enrolled into this study will receive one of the following treatments according to the randomization schedule:

- *Telithromycin*: 800 mg once daily (qd) orally for 7 to 10 days for CAP or AECB (treatment duration to be specified by the investigator), or 800 mg once daily orally for 5 days for AS. Each 800 mg dose will be administered as two 400 mg tablets. In subjects with known severe renal impairment (creatinine clearance <30 mL/min), the dose will be reduced to 400 mg (i.e., 1 tablet) qd.
- *Amoxicillin/clavulanic acid*: 875/125 mg orally twice daily (bid) for 7 to 10 days for CAP, AECB or AS (treatment duration to be specified by the investigator). Each 875/125 mg dose will be administered as one 875/125 mg tablet. In subjects with known severe renal impairment, the dose of amoxicillin will be reduced to 500 mg bid if creatinine clearance is between 10 and 30 mL/min, and to 500 mg qd if creatinine clearance is <10 mL/min. 500/125 mg tablets will be used for these subjects.

Telithromycin and amoxicillin/clavulanic acid (AMC) will be supplied by Aventis Pharmaceuticals, except for the AMC 500/125 mg tablets, which will be prescribed by the investigator as the commercially available product. All other medications are considered concomitant medications and are to be procured by the physician or subject utilizing the commercially available product.

5.3 TREATMENT ASSIGNMENT

The investigational products will be administered only to subjects included in this study following the procedures set out in the clinical study protocol.

Subjects enrolled in the study and meeting all of the inclusion criteria and none of the exclusion criteria will be assigned a unique subject number. This subject number will be used to identify the subject throughout the study, and will consist of a 4-digit site number and a 3-digit sequential number starting with 001 for each subject. Subjects withdrawn from the study retain their subject number and their randomization number, if already given. New subjects must always be allotted a new subject number and a new randomization number.

Randomization will occur through the use of the central telephone program Interactive Voice Response System (IVRS) after the subject has met all eligibility criteria. The following information will be provided by the site to the IVRS before randomization can take place:

- 4-digit site number
- Subject's initials
- Subject's date of birth
- Type of infection (must be CAP, AECB or AS)
- Renal function status (known to be severely impaired [creatinine clearance <30 mL/min] or not severely impaired [creatinine clearance ≥30 mL/min])

Subjects diagnosed with CAP or AECB and randomized to telithromycin will each receive two cartons, each containing one bottle with 10 tablets of 400 mg telithromycin (except in the case of subjects with known severe renal impairment, for whom the dosage of telithromycin will be reduced—see *Section 5.4.1*) for 7 to 10 days of treatment. The investigator must give subjects with CAP or AECB specific instructions on the duration of treatment (7 to 10 days) at the time when telithromycin is dispensed. Subjects diagnosed with AS and randomized to telithromycin will each receive a carton containing one bottle with 10 tablets of 400 mg telithromycin (except in the case of subjects with known severe renal impairment, for whom the dosage of telithromycin will be reduced—see *Section 5.4.1*) for 5 days of treatment. In all cases, the tear-off label on the carton(s) identifying the study medication will be removed and placed in the appropriate field on the case report form. Thus subjects with CAP or AECB will each have two labels placed in the case report form, while subjects with AS will each have one label placed in the case report form.

Subjects in all three indications randomized to amoxicillin/clavulanic acid (AMC) will receive a carton containing one bottle with 20 tablets of 875/125 mg AMC (except in the case of subjects with known severe renal impairment, for whom the dosage of AMC will be reduced and

500/125 mg AMC tablets will be used—see *Section 5.4.2*) for 7 to 10 days of treatment. The investigator must give the subjects specific instructions on the duration of treatment (7 to 10 days) at the time when AMC is dispensed. The tear-off label on the carton identifying the study medication will be removed and placed in the appropriate field on the case report form.

5.4 BLINDING, PACKAGING, AND LABELING

The investigational products will be packaged as open-label supplies by Aventis Pharmaceuticals or a designee except in the case of AMC 500/125 mg tablets (to be used for subjects with known severe renal impairment), which will be prescribed by the investigator as the commercial product (see *Section* 5.4.2).

5.4.1 Telithromycin

Telithromycin will be packaged in bottles containing 10 tablets of 400 mg telithromycin, with a label similar in format to the following example.

Aventis Pharmaceuticals Inc.
Route 202-206, Bridgewater, NJ 08807-0800
Tel.: 1 800 981 2491

Randomization Number: _____

10 tablets

Ketek™ tablets 400 mg
(Telithromycin)

For use in protocol HMR3647A/3014

Take as prescribed by your physician

Store at 25°C (77°F)
excursions permitted to 15-30°C (59-86°F)
(see USP Controlled Room Temperature)

For Use By: X/X/X

PR No: B0057

Caution: New Drug - Limited by Federal (or United States) law to investigational use.

The bottles will in turn be packed in cartons with a two-part tear-off label, which will be used to identify the study medication in the case report form, similar in format to the following example.

Aventis Pharmaceuticals Inc. Route 202-206, Bridgewater, NJ 08807-0800 Tel.: 1 800 981 2491 Randomization Number: _____ **10 tablets** **Ketek™ tablets 400 mg** (Telithromycin) **For use in protocol HMR3647A/3014** Store at 25°C (77°F) excursions permitted to 15-30°C (59-86°F) (see USP Controlled Room Temperature) For Use By: X/X/X PR No: B0057 Caution: New Drug - Limited by Federal (or United States) law to investigational use.	Aventis Pharmaceuticals Inc. Route 202-206, Bridgewater, NJ 08807-0800 Tel.: 1 800 981 2491 Randomization Number: _____ Each bottle contains **Ketek™ Tablets 400 mg**

Subjects with known severe renal impairment (see *Section 5.2*) will be given bottles containing either 10 tablets of 400 mg telithromycin (for 7- to 10-day treatment of CAP or AECB) or 5 tablets of 400 mg telithromycin (for 5-day treatment of AS) and instructed by the investigator to take only one tablet qd. In these cases the investigator will be responsible for removing the excess tablets from the standard cartons containing study medication. These excess tablets will be stored in an appropriate container and returned to the sponsor at the end of the study together with unused supplies of study medication.

Additional statements will be printed on the label(s) as required by local regulations.

5.4.2 Amoxicillin/clavulanic acid

Amoxicillin/clavulanic acid (AMC) will be supplied as the commercial product, which is packaged in bottles containing 20 tablets of 875/125 mg AMC. Each bottle will be given an additional label similar in format to the following example.

Aventis Pharmaceuticals Inc. Route 202-206, Bridgewater, NJ 08807-0800 Tel.: 1 800 981 2491 Randomization Number: _____ **For use in protocol HMR3647A/3014** PR No: B0057

The bottles will in turn be packed in cartons, with each carton containing the supply of study medication for a single subject participating in the study for the 7- to 10-day treatment of CAP, AECB or AS (i.e., a total of 20 tablets). The cartons will have a two-part tear-off label, which will be used to identify the study medication in the case report form, similar in format to the following example.

Aventis Pharmaceuticals Inc. Route 202-206, Bridgewater, NJ 08807-0800 Tel.: 1 800 981 2491 Randomization Number: _____ **Augmentin® tablets 875/125 mg** (Amoxicillin/clavulanate potassium) **For use in protocol HMR3647A/3014** Store at 25°C (77°F) excursions permitted to 15-30°C (59-86°F) (see USP Controlled Room Temperature) For Use By: X/X/X PR No: B0057 Caution: New Drug - Limited by Federal (or United States) law to investigational use..	Aventis Pharmaceuticals Inc. Route 202-206, Bridgewater, NJ 08807-0800 Tel.: 1 800 981 2491 Randomization Number: _____ Each bottle contains **Augmentin® Tablets** **875/125 mg**

Subjects with known severe renal impairment (see *Section 5.2*) will be treated with amoxicillin/clavulanic acid 500/125 mg tablets, which will be prescribed by the investigator as the commercially available product (Augmentin® 500/125). Because the 500/125 mg tablets will not be labeled and supplied by the sponsor, investigators will be issued with vouchers containing a two-part tear-off label, similar in format to the label shown above for the 875/125 mg tablets. To identify treatment with the 500/125 mg tablets, the tear-off portion of the label will be removed and placed in the appropriate field on the case report form. The remainder of the voucher will be returned to the sponsor's representative (CRO) for reimbursement of the cost of the medication.

Additional statements will be printed on the label(s) as required by local regulations.

5.5 SUPPLIES AND ACCOUNTABILITY

The investigator or pharmacist will inventory and acknowledge receipt of all shipments of the investigational products. The investigational products must be kept in a locked area with restricted access. The investigational products must be stored and handled in accordance with the manufacturer's instructions. The investigator or pharmacist will also keep accurate records of the quantities of the investigational products dispensed and (if applicable) returned by each subject. The study monitor, while visiting the site, will check the supplies of investigational products held by the investigator or pharmacist to verify accountability of all investigational products used. At

the conclusion of the study, all unused investigational products and all medication containers will be returned to the sponsor unless other arrangements have been approved by the sponsor. The sponsor will verify that a final report of drug accountability to the unit dose level is prepared and maintained in the investigator study file.

5.6 COMPLIANCE

The dates of first and last doses of study medication will be documented on the case report form at Visit 2.

Missed doses of study medication will not be documented.

6 PRIOR AND CONCOMITANT ILLNESSES AND TREATMENTS

6.1 PRIOR AND CONCOMITANT ILLNESSES

Selected additional illnesses (as specified in the case report form) present at the time informed consent is given are regarded as concomitant illnesses and must be documented in the case report form.

Illnesses first occurring or detected during the study, and worsening of a concomitant illness during the study, are to be regarded as adverse events and must be documented as such in the case report form (see *Section 8*).

6.2 PRIOR AND CONCOMITANT TREATMENTS

All treatments being taken by the subjects on entry to the study or at any time during the study in addition to the investigational product are regarded as concomitant treatments and must be documented on the appropriate pages of the case report form.

The following concomitant treatments are not permitted during this study:

- Ergot alkaloid derivatives, terfenadine, cisapride, astemizole, pimozide.

The following concomitant treatments are permitted with precautions during this study:

- Iron supplements or iron-containing drugs need to be separated by 2 hours in subjects randomized to telithromycin.
- Probenecid or allopurinol in subjects randomized to amoxicillin/clavulanic acid (as described under *Precautions* in the US labeling for Augmentin®, available in *Appendix A* of this protocol).

7 STUDY PROCEDURES AND SCHEDULE

7.1 OVERVIEW OF DATA COLLECTION

Safety will be evaluated on the basis of serious and non-serious adverse events. At Visits 2 and 3, the investigator will determine if serious adverse events (SAEs) or adverse events of special interest occurred. The occurrence of an SAE or an adverse event of special interest will prompt a follow-up investigation, as outlined in an "Adverse event of interest" form provided to the investigator. (see *Section 8.1.4*). Clinical laboratory tests will be conducted at Visit 1 (baseline) and Visit 2.

Effectiveness will be evaluated on the basis of the occurrence of hospitalization and whether hospitalization was for a complication of the primary infection or for an adverse event, whether an additional antibiotic needed to be prescribed to treat the primary infection, and the time lost from work (if the subject is employed).

The study procedures for each study day are described in *Section 7.2*, the methods of assessment in *Section 7.3*, and the analysis variables in *Section 11.1*.

7.2 DESCRIPTION OF STUDY DAYS

The study duration will be approximately one month and will include three scheduled visits.

Visit 1 and Visit 2 will involve the subjects attending the clinic, while Visit 3 will be performed either as a telephone visit or with the subjects attending the clinic (at the investigator's discretion, or depending on whether a serious adverse event or an adverse event of special interest occurred at Visit 2—see *Section 8.1.4*). The visits can be summarized as follows:

- **Visit 1** (Day 1, pre-therapy/entry): Screening, including informed consent and clinical laboratory tests, randomization, dispense and start treatment with study medication.
- **Visit 2** (Day 17 to 22, post-therapy): Document dates of first and last dose of study medication, conduct clinical laboratory tests, evaluate safety and effectiveness.
- **Visit 3** (Day 30 to 35, late post-therapy): Evaluate safety and effectiveness.

7.2.1 Screening

Screening will be performed at Visit 1, when the subjects enrolled into the study will also start their course of treatment with the study medication (Day 1). The following will be performed:

- Obtain signed informed consent.
- Check conformity to the inclusion/exclusion criteria.
- Take medical history, including in particular cardiovascular disease, chronic pulmonary disease, renal or hepatic impairment, demographics (age, race, sex).

- Document use of concomitant medication.
- Document antibiotic use in the previous 7 days.
- Conduct clinical laboratory tests (ALT, AST, total bilirubin, alkaline phosphatase).
- Conduct pregnancy test for women of childbearing potential (urine test).

7.2.2 Study days

Study days are numbered in relation to the first dose of study medication on Day 1.

Visit 1 (Day 1, pre-therapy/entry):

- Screening (see *Section 7.2.1*).
- Randomization to telithromycin or amoxicillin/clavulanic acid.
- Dispense and start taking the study medication.
- Schedule a return visit to the clinic for Visit 2 between Days 17 and 22.

Visit 2 (Day 17 to 22, post-therapy):

- Document date of first and last dose of study medication in the case report form.
- Document use of concomitant medication.
- Document any laboratory testing or ECGs performed.
- Conduct clinical laboratory tests (ALT, AST, total bilirubin, alkaline phosphatase).
- Evaluate safety by asking subjects if they have experienced any adverse events and by conducting a physical assessment. The occurrence of a serious adverse event or an adverse event of special interest will prompt a follow-up investigation, as outlined in an "Adverse event of interest" form provided to the investigator (see *Section 8.1.4*).
- Evaluate effectiveness by means of the occurrence of hospitalization and whether hospitalization was for a complication of the primary infection or for an adverse event, whether an additional antibiotic needed to be prescribed to treat the primary infection (name of antibiotic and date of start of treatment), and the time lost from work (if the subject is employed).
- Either instruct subjects that they will receive a telephone call on Day 30 to 35 for the Visit 3 evaluation or schedule a return visit to the clinic for Visit 3 (subjects must attend the clinic for Visit 3 if a serious adverse event or an adverse event of special interest was recorded at Visit 2).

Visit 3 (Day 30 to 35, late post-therapy):

- Document use of concomitant medication.
- Document any laboratory testing or ECGs performed.

- Evaluate safety by asking subjects if they have experienced any adverse events. The occurrence of a serious adverse event or an adverse event of special interest will prompt a follow-up investigation, as outlined in an "Adverse event of interest" form provided to the investigator (see *Section 8.1.4*). Subjects having a telephone visit who have experienced a serious adverse event or an adverse event of special interest will be required to attend the clinic for a follow-up investigation (which will be treated as a component of Visit 3). If there are symptoms of a hepatic adverse event of special interest, then follow-up laboratory investigations will be conducted in the clinic as recommended in general medical practice.
- Evaluate effectiveness by means of the occurrence of hospitalization and whether hospitalization was for a complication of the primary infection or for an adverse event, whether an additional antibiotic needed to be prescribed to treat the primary infection (name of antibiotic and date of start of treatment), and the time lost from work (if the subject is employed).

7.2.3 End of study

In the absence of SAEs or adverse events of special interest during the adverse event observation period (see *Section 8.2*), the subject's participation in this study ends with Visit 3.

In the presence of SAEs or adverse events of special interest during the adverse event observation period, the subject's participation in this study will end 35 days after the last dose of study medication or 30 days after the last visit (whichever is the later), when a follow-up telephone call will be made, or until the event has been resolved.

7.2.4 Follow-up

If an SAE occurs after the end of the adverse event observation period and is considered by the investigator to be possibly related to the study medication, the subject will be followed up as described in *Section 8.2*.

7.3 METHODS

7.3.1 Evaluation of safety

The safety assessment will be based on the evaluation of adverse events (AEs) and clinical laboratory tests as follows:

- AEs will be documented by the investigator or designee, who will determine if the subject experienced any serious AEs (SAEs) or AEs of special interest.
- Clinical laboratory tests will comprise ALT, AST, total bilirubin and alkaline phosphatase, but only ALT ≥3 x upper limit of the normal range will be considered an AE of special interest.
- SAEs, including SAEs of special interest, will be reported as described in *Section 8.4*. In addition, if any non-serious AEs of special interest occurred, the "Adverse Event" page in the

case report form will be completed by the investigator or designee and sent by fax to the sponsor's representative (CRO) within five working days.

- In case of SAEs or AEs of special interest, further information, such as physical examinations, vital signs, 12-lead electrocardiogram (ECG) and clinical laboratory reports, will be documented on an "Adverse event of interest" form provided to the investigator and sent by fax to the sponsor's representative (CRO) within five working days.
- An ongoing review of the AEs of special interest will be performed periodically by a Clinical Events Assessment Committee of external experts. The cases will be presented to the committee in a blinded fashion for initial review and adjudication. In addition to the investigators' assessments of the AEs of special interest, the committee will assess the nature of the events and any possible relationship to the study medication.

7.3.2 Evaluation of effectiveness

Effectiveness will be evaluated as follows:

- Occurrence of hospitalization and whether hospitalization was for a complication of the primary infection or for an adverse event.
- Whether or not an additional antibiotic needed to be prescribed to treat the primary infection.
- Time lost from work (if the subject is employed).

8 ADVERSE EVENTS

8.1 DEFINITIONS

8.1.1 Adverse event

The term **adverse event** covers any unfavorable and unintended sign, symptom, syndrome, or illness that develops or worsens during the period of observation in the clinical study. Clinically relevant abnormal results of diagnostic procedures including abnormal laboratory findings (e.g., requiring unscheduled diagnostic procedures or treatment measures, or resulting in withdrawal from the study) are considered to be adverse events.

Worsening of a sign or symptom of the condition under treatment will normally be measured by efficacy parameters. However, if the outcome fulfils the definition of "serious adverse event", it must be recorded as such (see *Section 8.1.2*).

The adverse event may be:

- A new illness
- Worsening of a concomitant illness
- An effect of the study medication, including comparator
- A combination of two or more of these factors

No causal relationship with the study medication or with the clinical study itself is implied by the use of the term "adverse event".

Adverse events fall into the categories "non serious" and "serious" (see *Section 8.1.2*).

Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an adverse event, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not adverse events, if the condition(s) was (were) known before the start of study treatment. In the latter case the condition should be reported as medical history.

8.1.2 Serious adverse event

A serious adverse event is one that at any dose (including overdose):

- Results in death

- Is life-threatening[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity[2]
- Is a congenital anomaly or birth defect
- Is an important medical event[3]

Clarification of the difference in meaning between "severe" and "serious"
The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.1.3 Other reasons for expedited reporting to Pharmacovigilance

Cases in which a "significant overdose" of the investigational product (definition at the investigator's discretion) was taken and a non-serious adverse event or no adverse event occurred are to be reported to the sponsor's representative (CRO) in an expedited manner on a "Serious Adverse Event/Expedited Report from a Clinical Trial" form.

In addition, any pregnancy diagnosed during treatment with the investigational product must be reported to the sponsor's representative (CRO) immediately. Information related to the pregnancy

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[1] "Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2] "Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

[3] Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A diagnosis of cancer during the course of a treatment should be considered as medically important. The List of Critical Terms (1998 adaptation of WHO Adverse Reaction Terminology Critical Terms List, provided in the "Instructions for completing the 'Serious Adverse Event/Expedited Report from a Clinical Trial' form") should be used as guidance for adverse events that may be considered serious because they are medically important.

must be given on a "Drug Exposure Via Parent – Data Collection" form that will be provided by the sponsor's representative (CRO).

8.1.4 Adverse events of special interest

Adverse events of special interest are to be documented on the "Adverse Event" page included in the case report form; this "Adverse Event" page must then be sent by fax to the sponsor's representative (CRO) within five working days (if non-serious). If serious, adverse events of special interest will be reported within 24 hours as described in *Section 8.4*. Adverse events of special interest include:

- Hepatic: reports of hepatitis, jaundice, worsening of a pre-existing hepatic condition, or ALT ≥3 x upper limit of the normal range.
- Cardiac: torsades de pointes, ventricular arrhythmias, syncope as defined by total loss of consciousness, cardiac arrest, or unwitnessed or unexplained death.
- Vasculitis: purpura or other signs of vasculitis.
- Visual: blurred vision.

The occurrence of an adverse event of special interest will prompt an appropriate follow-up investigation, including diagnostic work-up (e.g., physical examinations, vital signs, 12-lead electrocardiogram [ECG] and clinical laboratory reports), and subject medical record and consultation assessments, as outlined in an "Adverse event of interest" form provided to the investigator. This form must then be sent by fax to the sponsor's representative (CRO) within five working days.

Any subject with a serious adverse event or an adverse event of special interest at Visit 2 will be required to attend the clinic for Visit 3 (i.e., Visit 3 may not be conducted as a telephone visit). Subjects having a telephone visit at Visit 3 who have symptoms evoking a serious adverse event or an adverse event of special interest will be required to attend the clinic for the follow-up investigation (which will be treated as a component of Visit 3).

In the case of ALT ≥3 x upper limit of the normal range at Visit 2 (unless this is a decrease from a higher baseline value), follow-up laboratory investigations will be conducted as recommended in general medical practice. Likewise, if there are symptoms of a hepatic adverse event of special interest at Visit 3 (which may be a telephone or a clinic visit, and has no routine clinical laboratory tests), then follow-up laboratory investigations will also be conducted as recommended in general medical practice.

A review of the adverse events of special interest will be performed periodically by a Clinical Events Assessment Committee of external experts. The cases will be presented to the committee in a blinded fashion for initial review and adjudication.

8.2 PERIOD OF OBSERVATION

For the purposes of this study, the period of observation for collection of adverse events extends from the start of treatment with study medication (Day 1) until Visit 3 (Day 30 to 35).

All subjects who experience serious adverse events or adverse events of special interest during the period of observation must be followed up until resolution of the events. They will receive a follow-up telephone call 35 days after their last dose of study medication or 30 days after their last visit (whichever is the later), with further follow-up measures being taken for cases that have not been resolved during this time period.

If the investigator detects a serious adverse event in a study subject after the end of the period of observation, and considers the event possibly related to prior study treatment, he or she should contact the sponsor's representative (CRO) to determine how the adverse event should be documented and reported.

8.3 DOCUMENTATION AND REPORTING OF ADVERSE EVENTS BY INVESTIGATOR

All adverse events that occur during the observation period set in this protocol (see *Section 8.2*) must be documented on the pages provided in the case report form in accordance with the instructions for the completion of adverse event reports in clinical studies. These instructions are provided in the investigator's study file and/or in the case report form itself.

The following approach will be taken for documentation:

- **All adverse events** (whether serious or non-serious) must be documented on the "Adverse Event" page of the case report form.
- If the adverse event is serious (see *Section 8.1.2*), the investigator must complete, in addition to the "Adverse Event" page in the case report form, a "Serious Adverse Event/Expedited Report from a Clinical Trial" form at the time the serious adverse event is detected. This form must be sent to the sponsor's representative (CRO), who will forward it to the sponsor's Pharmacovigilance department.
- If adverse events of special interest occurred, the "Adverse Event" page in the case report form will be completed by the investigator or designee and sent by fax directly to the sponsor's representative (CRO) within five working days. The occurrence of an adverse event of special interest will prompt a follow-up investigation, as outlined in an "Adverse event of interest" form provided to the investigator (see *Section 8.1.4*) This form must then be sent by fax to the sponsor's representative (CRO) within five working days.
- When a "significant overdose" of the investigational product occurs without an adverse event (see *Section 8.1.3*), the investigator should only complete a "Serious Adverse Event/Expedited Report from a Clinical Trial" form. Instructions on where to send this form will be provided by the sponsor. In this case, there is no need to complete the "Adverse Event" page in the case report form.

Every attempt should be made to describe the adverse event in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

All subjects who have adverse events, whether considered associated with the use of the investigational products or not, must be monitored to determine the outcome. The clinical course of the adverse event will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up. Should the adverse event result in death, a full pathologist's report should be supplied, if possible.

All questions on the completion and supply of adverse event report forms and any further forms issued to the investigator at a later date to clarify unresolved issues should be addressed to the sponsor or to the sponsor's representative (CRO).

8.4 IMMEDIATE REPORTING BY INVESTIGATOR TO SPONSOR

Serious adverse events and adverse events that fulfill a reason for expedited reporting to Pharmacovigilance (as defined in *Section 8.1.3*) must be documented on a "Serious Adverse Event/Expedited Report from a Clinical Trial" form in accordance with the "Instructions for completing the 'Serious Adverse Event/Expedited Report from a Clinical Trial' form". This form must be completed and supplied to the sponsor within 24 hours, or at the latest on the following working day. The "Serious Adverse Event/Expedited Report from a Clinical Trial" form and the instructions are provided in the investigator's study file.

The investigator must also inform the study monitor in all cases. The sponsor will ensure that all legal reporting requirements are met.

The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s).

Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up "Serious Adverse Event/Expedited Report from a Clinical Trial" form.

The "Instructions for completing the 'Serious Adverse Event/Expedited Report from a Clinical Trial' form" give more detailed guidance on the reporting of serious adverse events and adverse events initially reported as non-serious that become serious. In the latter situation, when a non-serious event becomes serious, details must be forwarded immediately to the sponsor on a "Serious Adverse Event/Expedited Report from a Clinical Trial" form.

Adverse events of special interest should be forwarded to the sponsor's representative (CRO) within five working days (see *Section 8.1.4*).

9 WITHDRAWALS

9.1 WITHDRAWAL OF SUBJECTS

Subjects may be withdrawn from the study (i.e. from any further study medication or study procedure) for the following reasons:

- At their own request or at the request of their legally authorized representative[4]
- If, in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being
- At the specific request of the sponsor

In all cases, the reason for and date of withdrawal must be recorded in the case report form and in the subject's medical records and the sponsor's representative must be notified within 5 days. The subject must be followed up to establish whether the reason was an adverse event, and, if so, this must be reported in accordance with the procedures in *Section 8*.

As far as possible, subjects who fail to complete the specified course of treatment with study medication should still participate in Visits 2 and 3.

The investigator must make every effort to contact subjects lost to follow-up. Attempts to contact such subjects must be documented in the subject's records (e.g., dates and times of attempted telephone contact).

9.2 REPLACEMENT OF SUBJECTS

Subjects will not be replaced.

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[4] "Legally authorized representative" means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

10 EMERGENCY PROCEDURES

10.1 EMERGENCY SPONSOR CONTACT

In emergency situations, the investigator should contact the sponsor by telephone at the number given on the title page of the protocol.

10.2 EMERGENCY IDENTIFICATION OF INVESTIGATIONAL PRODUCTS

This section is not applicable as this is an open-label study.

10.3 EMERGENCY TREATMENT

During and after a subject's participation in the trial, the investigator and/or institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator and/or institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

11 STATISTICAL PROCEDURES

11.1 ANALYSIS VARIABLES

The **safety** analysis variables will include rates of serious and non-serious adverse events occurring during the 30-day study period.

The **effectiveness** analysis variables will be:

- Hospitalization due to infection and whether the hospitalization was for a complication of the primary infection or for an adverse event.
- Prescription of an additional antibiotic to treat the primary infection (name of antibiotic and date of start of treatment).
- Work productivity if the subject is employed (days lost from work).

11.2 ANALYSIS POPULATIONS

Safety: All subjects who received at least one dose of study medication and who had at least one post baseline safety assessment.

Effectiveness: Intent-to-treat (ITT) population, which is defined as the population of subjects that were randomized.

11.3 STATISTICAL METHODS

Safety and effectiveness data from approximately 24,000 subjects will be evaluated (12,000 subjects treated with telithromycin and 12,000 subjects treated with comparator). An interim analysis will be carried out after the first 6,000 subjects treated with telithromycin have completed the study.

Complete details of the statistical analyses and methods, including data conventions, will be contained in a separate statistical analysis plan that will be finalized before the database is locked.

11.3.1 Analysis of baseline data

Baseline demographic and clinical variables will be summarized.

Analysis of safety data

The safety analysis will include rates of serious and non-serious adverse events occurring during the 30-day study period. Confidence interval estimates for event rates will be calculated. Event rates will also be summarized by subpopulations of subjects potentially at risk, including women,

older subjects (≥50 years), subjects with renal or hepatic impairment, subjects with cardiovascular or chronic respiratory diseases, and subjects taking selected concomitant medications.

Analysis of effectiveness data

Summary statistics and confidence intervals will be determined by treatment group for each of the effectiveness variables. Comparisons will be made between treatment groups to establish the clinical non-inferiority of telithromycin, with the comparison of special interest being rates of hospitalization in subjects ≥50 years.

11.4 INTERIM ANALYSIS

An interim analysis will be carried out after the first 6,000 subjects treated with telithromycin have completed the study.

11.5 SAMPLE SIZE JUSTIFICATION

With a given rare event occurring at a rate of 1/10,000 in the general population, if no events are observed in the interim analysis on the first 6,000 subjects treated with telithromycin, a three-fold increase in this background risk of the event in the telithromycin group can be excluded with 83% confidence and a two-fold increase can be excluded with 70% confidence. In the final analysis on 12,000 subjects treated with telithromycin, the corresponding confidence levels are 98% and 91%, respectively, if no events are observed, and 85% and 70%, respectively, if one event is observed.

In the effectiveness analyses, the subgroup of subjects ≥50 years of age is of special interest. The number of subjects in this subgroup is expected to be approximately 2,000 per treatment group in the interim analysis and 4,000 subjects per treatment group in the final analysis. Assuming a hospitalization rate of 3% in each treatment group, non-inferiority of telithromycin can be demonstrated with 80% power in the interim analysis and with 90% power in the final analysis, using a non-inferiority margin of 1.5%. This approach takes into consideration adjustment of individual confidence levels to maintain an overall confidence level of 95% across multiple endpoints, as specified in the analysis plan.

12 ETHICAL AND LEGAL ASPECTS

12.1 GOOD CLINICAL PRACTICE

This study is to be conducted according to globally accepted standards of good clinical practice (as defined in the ICH E6 Guideline for Good Clinical Practice, 1 May 1996), in agreement with the latest locally applicable revision of the Declaration of Helsinki and in keeping with local regulations.

12.2 DELEGATION OF INVESTIGATOR DUTIES

The investigator should ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

The investigator should maintain a list of subinvestigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

12.3 SUBJECT INFORMATION AND INFORMED CONSENT

Before being enrolled in the clinical study, subjects must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to them.

An informed consent document that includes information about the study will be prepared and given to the subject. This document will contain all the elements required by the ICH E6 Guideline for Good Clinical Practice and any additional elements required by local regulations. The document must be in a language understandable to the subject and must specify who informed the subject. Where required by local law, the person who informs the subject must be a physician.

After reading the informed consent document, the subject must give consent in writing. The subject's consent must be confirmed at the time of consent by the personally dated signature of the subject and by the personally dated signature of the person conducting the informed consent discussions.

A copy of the signed consent document must be given to the subject. The original signed consent document will be retained by the investigator.

The investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

The investigator should inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

12.4 CONFIDENTIALITY

Subject names will not be supplied to the sponsor. Only the subject number and subject initials will be recorded in the case report form, and if the subject name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of the sponsor, independent ethics committee (IEC)/ institutional review board (IRB), or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

12.5 PROTOCOL AMENDMENTS

Neither the investigator nor the sponsor will alter this clinical study protocol without obtaining the written agreement of the other. Once the study has started, amendments should be made only in exceptional cases. The changes then become part of the clinical study protocol.

12.6 APPROVAL OF THE CLINICAL STUDY PROTOCOL AND AMENDMENTS

Before the start of the study, the clinical study protocol, informed consent document, and any other appropriate documents will be submitted to the IEC/IRB with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities, in accordance with local legal requirements.

Investigational products can only be supplied to the investigator after documentation on **all** ethical and legal requirements for starting the study has been received by the sponsor. This documentation must also include a list of the members of the IEC/IRB and their occupation and qualifications. If the IEC/IRB will not disclose the names of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. Formal approval by the IEC/IRB should preferably mention the study title, study code, study site (or region or area of jurisdiction, as applicable), amendment number where applicable, and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member.

Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IEC/IRB and, if applicable, the authorities must be informed of all subsequent protocol amendments and administrative changes, in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

The investigator must keep a record of all communication with the IEC/IRB and, if applicable, between a coordinating investigator and the IEC/IRB. This also applies to any communication between the investigator (or coordinating investigator, if applicable) and the authorities.

12.7 ONGOING INFORMATION FOR INDEPENDENT ETHICS COMMITTEE/ INSTITUTIONAL REVIEW BOARD

Unless otherwise instructed by the IEC/IRB, the investigator must submit to the IEC/IRB:

- Information on serious or unexpected adverse events from the investigator's site, as soon as possible
- Expedited safety reports from the sponsor, as soon as possible
- Periodic reports on the progress of the study

12.8 CLOSURE OF THE STUDY

The study must be closed at the site on completion. Furthermore, the sponsor or the investigator has the right to close this study site at any time. As far as possible, premature closure should occur after mutual consultation. Depending on local legislation, it may be necessary to inform IEC/IRB and the regulatory authorities when the study site is closed.

Study materials must be returned, disposed of or retained as directed by the sponsor.

12.9 RECORD RETENTION

The investigator must obtain approval in writing from the sponsor before destruction of any records.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, because of international regulatory requirements, the sponsor may request retention for a longer period.

Essential documents include:

- Signed informed consent documents for all subjects
- Subject identification code list*, screening log (if applicable) and enrollment log
- Record of all communications between the investigator and the IEC/IRB

- Composition of the IEC/IRB (or other applicable statement as described in *Section 12.6*)
- Record of all communications between the investigator and sponsor (or CRO)
- List of subinvestigators and other appropriately qualified persons to whom the investigator has delegated significant trial-related duties, together with their roles in the study and their signatures
- Copies of case report forms and of documentation of corrections for all subjects
- Investigational product accountability records
- Record of any body fluids or tissue samples retained
- All other source documents (subject medical records, hospital records, laboratory records, etc.)
- All other documents as listed in section 8 of the ICH E6 Guideline for Good Clinical Practice (Essential Documents for the Conduct of a Clinical Trial)

Normally, these records will be held in the investigator's archives. If the investigator is unable to meet this obligation, he or she must ask the sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.

*EU legislation requires this list to be maintained for a minimum of 15 years

12.10 LIABILITY AND INSURANCE

Liability and insurance provisions for this study are given in separate agreements.

13 STUDY MONITORING AND AUDITING.

Monitoring and auditing procedures developed or endorsed by the sponsor will be followed, in order to comply with GCP guidelines. Direct access to the on-site study documentation and medical records must be ensured.

13.1 STUDY MONITORING AND SOURCE DATA VERIFICATION

Monitoring will be done according to the monitoring plan by a representative of the sponsor (study monitor) who will check the case report forms for completeness and clarity, and crosscheck them with source documents. In addition to the monitoring visits, frequent communications (letter, telephone, fax, e-mail), by the study monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements.

Study close-out will be performed by the study monitor upon closure of the study.

13.2 ON-SITE AUDITS

Domestic and foreign regulatory authorities, the IEC/IRB, and an auditor authorized by the sponsor may request access to all source documents, case report forms, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities. Medical records and other study documents may be copied during audit or inspection provided that subject names are obliterated on the copies to ensure confidentiality.

14 DOCUMENTATION AND USE OF STUDY FINDINGS

14.1 DOCUMENTATION OF STUDY FINDINGS

A case report form will be provided for each subject.

All protocol-required information collected during the study must be entered by the investigator, or designated representative, in the case report form. Details of case report form completion and correction will be explained to the investigator. If the investigator authorizes other persons to make entries in the case report form, the names, positions, signatures, and initials of these persons must be supplied to the sponsor.

The investigator, or designated representative, should complete the case report form pages as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

A source data location list will be prepared prior to study start. This list will be filed in both the trial master file and the investigator study file and updated as necessary.

The completed case report form must be reviewed and signed by the investigator named in the clinical study protocol or by a designated subinvestigator.

The sponsor will retain the originals of all case report forms. The investigator will retain a copy of all completed case report form pages.

14.2 USE OF STUDY FINDINGS

All information concerning the product as well as any matter concerning the operation of the sponsor, such as clinical indications for the drug, its formula, methods of manufacture and other scientific data relating to it, that have been provided by the sponsor and are unpublished, are confidential and must remain the sole property of the sponsor. The investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the sponsor is obtained.

The sponsor has full ownership of the original case report forms completed as part of the study.

By signing the clinical study protocol, the investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. The authorities will be notified of the investigator's name, address, qualifications, and extent of involvement.

The sponsor will ensure that a final report on the study is prepared.

The investigator (or coordinating investigator) will be required to sign a statement that he or she confirms that, to the best of his or her knowledge, it accurately describes the conduct and results of the study.

All materials, documents and information supplied by the sponsor to the investigator, and all materials, documents and information prepared or developed in the course of the study to be performed under this protocol, shall be the sole and exclusive property of the sponsor. Subject to obligations of confidentiality, the investigator reserves the right to publish only the results of the work performed pursuant to this protocol, provided, however, that the investigator provides an authorized representative of the sponsor with a copy of any proposed publication for review and comment at least 45 days in advance of its submission for publication. In addition, if requested, the investigator will withhold publication an additional 90 days to allow for filing a patent application or taking such other measures as sponsor deems appropriate to establish and preserve its proprietary rights.

It is agreed that, consistent with scientific standards, publication of the results of the study shall be made only as part of a publication of the results obtained by all sites performing the protocol.

15 DECLARATIONS OF SPONSOR AND INVESTIGATOR

15.1 DECLARATION OF SPONSOR

This clinical study protocol was subject to critical review and has been approved by the sponsor. The information it contains is consistent with:

- The current risk-benefit evaluation of the investigational product
- The moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the principles of GCP as described in 21 CFR parts 50, 54, 56, and 312 and according to applicable local requirements.

The investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

Clinical manager

Date 09/27/01 Signature: _____

Name (block letters): BRUNO LEROY, MD

15.2 DECLARATION OF INVESTIGATOR

I confirm that I have read the above protocol. I understand it, and I will work according to the principles of GCP as described in 21 CFR parts 50, 54, 56, and 312 and according to applicable local requirements.

Investigator

Date: _____ Signature: _____

Name (block letters): _____

16 REFERENCES

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APPENDIX A: DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The Purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined with Professional Care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient--including those of a control group, if any--should be assured of the best-proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee.

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-Therapeutic Biomedical Research Involving Human Subjects (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers--either healthy persons or patients for whom the experimental design is not related to the patient's illness.